

PATENT COOPERATION TREATY

PCT

REC'D 30 JUN 2005

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 53098AWO	FOR FURTHER ACTION		See Form PCT/IPEA/416																								
International application No. PCT/EP2004/007737	International filing date (day/month/year) 13.07.2004	Priority date (day/month/year) 28.07.2003																									
International Patent Classification (IPC) or national classification and IPC C07J43/00, A61K31/58, A61P15/08																											
Applicant SCHERING AKTIENGESELLSCHAFT et al.																											
<ol style="list-style-type: none"> 1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36. 2. This REPORT consists of a total of 7 sheets, including this cover sheet. 3. This report is also accompanied by ANNEXES, comprising: <ol style="list-style-type: none"> a. <input type="checkbox"/> sent to the applicant and to the International Bureau a total of sheets, as follows: <ul style="list-style-type: none"> <input type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions). <input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box. b. <input type="checkbox"/> (sent to the International Bureau only) a total of (Indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions). 																											
<ol style="list-style-type: none"> 4. This report contains indications relating to the following items: <table style="width: 100%; border: none;"> <tr> <td style="width: 10%;"><input checked="" type="checkbox"/></td> <td style="width: 15%;">Box No. I</td> <td>Basis of the opinion</td> </tr> <tr> <td><input type="checkbox"/></td> <td>Box No. II</td> <td>Priority</td> </tr> <tr> <td><input checked="" type="checkbox"/></td> <td>Box No. III</td> <td>Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</td> </tr> <tr> <td><input type="checkbox"/></td> <td>Box No. IV</td> <td>Lack of unity of invention</td> </tr> <tr> <td><input checked="" type="checkbox"/></td> <td>Box No. V</td> <td>Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</td> </tr> <tr> <td><input type="checkbox"/></td> <td>Box No. VI</td> <td>Certain documents cited</td> </tr> <tr> <td><input type="checkbox"/></td> <td>Box No. VII</td> <td>Certain defects in the international application</td> </tr> <tr> <td><input checked="" type="checkbox"/></td> <td>Box No. VIII</td> <td>Certain observations on the international application</td> </tr> </table> 				<input checked="" type="checkbox"/>	Box No. I	Basis of the opinion	<input type="checkbox"/>	Box No. II	Priority	<input checked="" type="checkbox"/>	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability	<input type="checkbox"/>	Box No. IV	Lack of unity of invention	<input checked="" type="checkbox"/>	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement	<input type="checkbox"/>	Box No. VI	Certain documents cited	<input type="checkbox"/>	Box No. VII	Certain defects in the international application	<input checked="" type="checkbox"/>	Box No. VIII	Certain observations on the international application
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Date of submission of the demand 21.12.2004	Date of completion of this report 29.06.2005																										
Name and mailing address of the International preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Telephone No. +49 89 2399- 7536 																										

4- **INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/EP2004/007737

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.
- ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
- ☐ international search (under Rules 12.3 and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4)
 - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)
2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-38 as originally filed

Claims, Numbers

1-12 as originally filed

Claims, Pages

39-43 as originally filed

Drawings, Sheets

1/6-6/6 as originally filed

Drawings, Figures

1-6 as originally filed

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):
4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):

* If item 4 applies, some or all of these sheets may be marked "superseded."

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/EP2004/007737

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:
- ☐ the entire international application,
 - ☒ claims Nos. 9-10
- because:
- ☒ the said international application, or the said claims Nos. 9-10 relate to the following subject matter which does not require an international preliminary examination (specify):
see separate sheet
 - ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
 - ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
 - ☐ no international search report has been established for the said claims Nos.
 - ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
 - the written form ☐ has not been furnished
 - ☐ does not comply with the standard
 - the computer readable form ☐ has not been furnished
 - ☐ does not comply with the standard
 - ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.
 - ☐ See separate sheet for further details

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/EP2004/007737

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-12
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	1-12
Industrial applicability (IA)	Yes: Claims	1-8, 11-12
	No: Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 9-10 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents (D):

- D1: EP-A-1 245 572 (SCHERING AG) 2 October 2002 (2002-10-02)
- D2: US-A-2 846 432 (NYSTED LEONARD N) 5 August 1958 (1958-08-05)
- D3: DE 19 30 473 A (SCHERING AG) 17 December 1970 (1970-12-17)
- D4: US-A-2 813 094 (NYSTED LEONARD N) 12 November 1957 (1957-11-12)
- D5: WO 99 45024 A (MARSDEN JOHN CHRISTOPHER ;HESSE ROBERT HENRY (US); RAMGOPAL MALATH) 10 September 1999 (1999-09-10)

The application refers to pharmaceutically active thiomorpholino steroid compounds suitable for the regulation of meiosis.

1) Article 33(2) PCT

Although steroidal compounds, where an heterocyclic moiety is bound through a bridging moiety to the 17-position of the steroidal skeleton, are known in the prior art, the claimed 2-(thiomorpholin-4-yl)-1-methyl-ethyl substitution at the C¹⁷ of the steroid skeleton is not explicitly disclosed in any of the cited prior art documents, rendering thus the subject matter of the present application as formally novel and therefore the present application can be considered as to fulfill the requirements of Article 33(2) PCT.

2) Article 33(3) PCT

The problem outlined in the present application is to provide compounds, which are useful in the regulation of meiosis. As the prior art (documents D1 and D5) has already dealt with this problem, the actual technical problem may be seen in the provision of **further** compounds capable of regulating the meiosis.

Alternative solutions to a known technical problem can be considered as inventive when it can be shown that they do not derive from the prior art in an obvious manner and that they indeed solve the problem eventually showing an unexpected effect.

With respect to the question whether the subject matter of the present application provides a "real" solution to the technical problem mentioned above, the biological tests provided in pages 26-38 and in particular tables 1-6 show that the disclosed examples do have the claimed activity.

With respect to the information given from the prior art and the question whether the solution provided by the present application can be derived in an obvious manner, the Examining Division considers the claimed compounds as structurally close related to the entities disclosed in the prior art, and that the minor modification, which distinguishes them from the latter can be regarded as part of the synthetic routine of the person skilled in the art when looking for alternative solutions:

document D1, which can be considered as the closest prior art, discloses structurally closest related compounds with the same activity, differing from the claimed compounds in that instead of a thiomorpholine ring they have a morpholine, piperazine, piperidine, pyrrolidine etc. ring. This same variation in the substitution at the 17-position is also disclosed in document D2 referring to structurally close related compounds having, however, a different activity. However, the exchange of the oxygen atom in the morpholine ring with a carbon, nitrogen or sulphur atom can be considered as common practice in the synthetic routine of the person skilled in the art when looking for alternative solutions. This fact, is supported by the prior art documents D3-D5:

- a) D3 defines in page 5 the R¹ and R² substitution, in case of them being a ring moiety, as a piperidine, pyrrolidine, morpholine, piperazine or thiomorpholine ring,
- b) D4 discloses for similar compounds, that the nitrogen containing heterocyclic radical mainly represents a morpholino radical but can also be a piperazino, N'-alkylpiperazino, thiomorpholino etc., and
- c) D5 discloses similar compounds, where for each example containing a morpholine ring also a corresponding example with a thiomorpholine ring is mentioned (examples 5/7 and 6/8, claims 5 and 9).

Since, as it was shown above, the variation in the atom of the 4-position of a nitrogen

containing 6-membered saturated ring belongs to the common practice of the person skilled in the art when looking for an alternative solution to a known and solved chemical problem, and on the basis of the information given by the document D1 for the structural core of meiosis regulating compounds, in which the thiomorpholine ring was the only one not explicitly disclosed among the ring possibilities bound to the C¹⁷ via the same alkylene spacer, the subject matter of the present application is considered as not to involve inventive ingenuity, and therefore does not fulfill the requirements of Article 33(3) PCT.

The applicant is informed that an inventive merit for the "selection" of the thiomorpholino substitution can only be acknowledged in the case that the claimed subject matter shows unexpected effects with respect to the closest prior art. Consequently, for a possible reconsideration regarding the evaluation of the inventive merit of the subject matter of the present application, further evidence will be needed, where the properties of the claimed compounds are compared with those of the structural more related compounds from D1.

3) Rule 67.1(iv) PCT

For the assessment of the present claims 9 and 10 (and the corresponding part of the description pages 6 and 15) on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VIII

Certain observations on the international application

When entering the regional phase before the EPO, the expression "the spirit of the invention" mentioned in page 34, line 27 can not be allowable under Rule 34 EPC, as it may imply a possible extension of the protection in some vague and not precisely defined way.